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Diphenhydramine Citrate and Ibuprofen Tablets

DEFINITION

Diphenhydramine Citrate and Ibuprofen Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of diphenhydramine citrate ($C_{17}H_{21}NO \cdot C_6H_8O_7$) and ibuprofen ($C_{13}H_{18}O_2$).

IDENTIFICATION

• **A.** The retention times of the diphenhydramine and ibuprofen peaks from the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Buffer A: 6.9 g/L of monobasic sodium phosphate in water

Buffer B: 6.9 g/L of monobasic sodium phosphate in water. Adjust with triethylamine to a pH of 7.2.

Mobile phase: Acetonitrile, triethylamine, glacial acetic acid, and *Buffer A* (45:0.2:0.2:55)

Diluent: Acetonitrile and *Buffer B* (3:2)

Standard solution: 1.1 mg/mL of USP Diphenhydramine Citrate RS and 5.7 mg/mL of USP Ibuprofen RS in *Diluent*. [Note—Sonicate as necessary.]

Sample solution: Transfer 10 Tablets into a suitable volumetric flask, add 350 mL of *Diluent*, and shake with a rotary shaker for 20 min. Sonicate for 20 min with intermediate shaking to obtain a solution containing about 1.1 mg/mL of diphenhydramine citrate and 5.7 mg/mL of ibuprofen. Centrifuge an aliquot at 4000 rpm for 10 min, and use the supernatant. [Note—Do not dilute to volume.]

Chromatographic system

(See *Chromatography (621), System Suitability*.)

Mode: LC

Detector: UV 260 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 1.2 mL/min

Injection size: 20 µL

Run time: 1.3 times the retention time of ibuprofen

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for both diphenhydramine and ibuprofen

Relative standard deviation: NMT 2.0% for both diphenhydramine and ibuprofen

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amounts of diphenhydramine citrate ($C_{17}H_{21}NO \cdot C_6H_8O_7$) and ibuprofen ($C_{13}H_{18}O_2$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of the corresponding analyte from the *Sample solution*

r_S = peak response of the corresponding analyte from the *Standard solution*

C_S = concentration of the appropriate USP Reference Standard in the *Standard solution* (mg/mL)

C_U = nominal concentration of the corresponding analyte in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0% for both diphenhydramine citrate and ibuprofen

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Medium: pH 6.5 phosphate buffer (Transfer 250 mL of 0.2 M monobasic potassium phosphate and 58 mL of 0.2 M sodium hydroxide to a 1000-mL volumetric flask, and dilute with water to volume.); 900 mL, deaerated

Apparatus 2: 50 rpm

Time: 30 min

Buffer solution: 6.9 g/L of sodium dihydrogen phosphate monohydrate in water

Ibuprofen standard stock solution: 1.1 mg/mL of USP Ibuprofen RS in acetonitrile

Diphenhydramine citrate standard stock solution: 1.1 mg/mL of USP Diphenhydramine Citrate RS in water

Standard solution: Transfer 5 mL of the *Ibuprofen standard stock solution* and 1 mL of *Diphenhydramine citrate standard stock solution* to a 25-mL volumetric flask, and dilute with *Medium* to volume.

Sample solution: Pass a portion of the solution under test through a suitable filter.

Mobile phase: Acetonitrile, triethylamine, glacial acetic acid, and *Buffer solution* (45:0.2:0.2:55)

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm, 5-µm packing L1

Flow rate: 1.2 mL/min

Injection size: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for both diphenhydramine and ibuprofen

Relative standard deviation: NMT 2.0% for both diphenhydramine and ibuprofen

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of diphenhydramine and ibuprofen dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times 100$$

r_U = peak response of ibuprofen or diphenhydramine from the *Sample solution*

r_S = peak response of ibuprofen or diphenhydramine from the *Standard solution*

C_S = concentration of ibuprofen or diphenhydramine in the *Standard solution*

L = label claim for ibuprofen or diphenhydramine (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (*Q*) of the labeled amounts of diphenhydramine and ibuprofen are dissolved.

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

• **Organic Impurities**

Buffer A: 1 mL of phosphoric acid in 1 L of water. Adjust with triethylamine to a pH of 3.2.

Buffer B: 1 mL of phosphoric acid and 1.0 g of monobasic potassium phosphate in 1 L of water. Adjust with triethylamine to a pH of 3.7.

Solution A: Acetonitrile and *Buffer A* (1:4)

Solution B: Acetonitrile and *Buffer B* (1:1)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
30	50	50
45	50	50
80	40	60
85	100	0
100	100	0

Standard solution: 0.004 mg/mL of USP Diphenhydramine Citrate RS and 0.02 mg/mL of USP Ibuprofen RS in *Solution B*

System suitability solution: 0.004 mg/mL of USP Diphenhydramine Related Compound A RS, 0.8 mg/mL of USP Diphenhydramine Citrate RS, and 4 mg/mL of USP Ibuprofen RS in *Solution B*

Sample solution: Transfer an amount of powder from ground Tablets (NLT 20) to a suitable volumetric flask. Add 70% of the flask volume of *Solution B*, sonicate for 20 min and dilute with *Solution B* to volume to obtain a solution containing about 0.8 mg/mL of diphenhydramine citrate and 4 mg/mL of ibuprofen. Centrifuge an aliquot at 4000 rpm for 10 min, and use the supernatant.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection size: 10 µL

System suitability

Samples: *Standard solution* and *System suitability solution*

Suitability requirements

Resolution: NLT 0.8 between diphenhydramine and diphenhydramine related compound A, *System suitability solution*

Tailing factor: NMT 2.0 for both diphenhydramine and ibuprofen, *Standard solution*

Relative standard deviation: NMT 5.0% for both diphenhydramine and ibuprofen, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Identify the ibuprofen and diphenhydramine impurities using the relative retention times given in *Table 2*. Calculate the percentage of each diphenhydramine impurity and unspecified impurities in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of diphenhydramine from the *Standard solution*

C_S = concentration of USP Diphenhydramine Citrate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of diphenhydramine citrate in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 2*)

Calculate the percentage of the ibuprofen related impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of the ibuprofen related impurity from the *Sample solution*

r_S = peak response of ibuprofen from the *Standard solution*

C_S = concentration of USP Ibuprofen RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of ibuprofen in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Diphenhydramine related compound A[a]	0.95	1.3	0.26
Diphenhydramine	1.00	1.0	—
Unidentified diphenhydramine degradation product	1.32	1.0	0.2
Unidentified diphenhydramine degradation product	1.46	1.0	0.2
Unidentified ibuprofen degradation product	1.49	1.0	0.1
Methyl ibuprofen[b,c]	1.86	—	—
Unidentified diphenhydramine degradation product	1.96	1.0	0.2
Benzhydryl bromide[d]	2.49	2.4	0.26
Ibuprofen amide[b,e]	2.87	—	—
Isopropyl ibuprofen[b,f]	3.45	—	—
n-Propyl ibuprofen[b,g]	3.71	—	—
meta-Ibuprofen[b,h]	5.09	—	—
Ibuprofen	5.31	—	—
n-Butyl ibuprofen[b,i]	5.68	—	—
Any other individual unspecified degradation product[j]	—	1.0	0.2
Total impurities[k]	—	—	1.0

[a] 2-(Diphenylmethoxy)-*N*-methylethanamine.

[b] Process impurity provided for information only; the content is not calculated and not reported.

[c] 2-*p*-Tolylpropanoic acid.

[d] (Bromomethylene)dibenzene.

[e] 2-(4-Isobutylphenyl) propanamide.

[f] 2-(4-Isopropylphenyl)propanoic acid.

[g] 2-(4-Propylphenyl)propanoic acid.

[h] 2-(3-Isobutylphenyl)propanoic acid.

[i] 2-(4-Butylphenyl)propanoic acid.

[j] Exclude peaks that elute before 4 min or after 80 min.

[k] Total impurities excludes ibuprofen related compound C.

- **Limit of Ibuprofen Related Compound C**

Buffer: 10 g/L of chloroacetic acid in water. Adjust with ammonium hydroxide to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (3:2)

Internal standard solution: 0.35 mg/mL of valerophenone in *Mobile phase*

Standard stock solution: 0.6 mg/mL of USP Ibuprofen Related Compound C RS in acetonitrile

Standard solution: 0.012 mg/mL of USP Ibuprofen Related Compound C RS in *Internal standard solution*; prepared by diluting 2 mL of *Standard stock solution* with *Internal standard solution* to 100 mL

Sample solution: Transfer an amount of powder equivalent to 1200 mg of ibuprofen from ground Tablets (NLT 20) to a suitable volumetric flask. Add 100 mL of *Internal standard solution*, and sonicate for 20 min to obtain a solution containing about 12 mg/mL of ibuprofen. Pass through a suitable filter, and use the filtrate. [Note—Do not dilute to volume.]

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 2 mL/min

Injection size: 5 µL

System suitability

Sample: *Standard solution*

[Note—The relative retention times for valerophenone and ibuprofen related compound C are 0.86 and 1.0, respectively.]

Suitability requirements

Tailing factor: NMT 2.5 for both valerophenone and ibuprofen related compound C

Relative standard deviation: NMT 2.0%

Resolution: NLT 2.5 between the valerophenone and ibuprofen related compound C peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ibuprofen related compound C ($C_{12}H_{16}O$) in the portion of Tablets taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = peak area ratio of ibuprofen related compound C to valerophenone from the *Sample solution*

R_S = peak area ratio of ibuprofen related compound C to valerophenone from the *Standard solution*

C_S = concentration of USP Ibuprofen Related Compound C RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of ibuprofen in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 0.1% of ibuprofen related compound C

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.
- **USP Reference Standards ⟨11⟩**

USP Diphenhydramine Citrate RS

USP Diphenhydramine Related Compound A RS

2-(Diphenylmethoxy)-*N*-methylethanamine hydrochloride.

$C_{16}H_{19}NO \cdot HCl$ 277.79

USP Ibuprofen RS

USP Ibuprofen Related Compound C RS

4-Isobutylacetophenone.

$C_{12}H_{16}O$ 176.25

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
DIPHENHYDRAMINE CITRATE AND IBUPROFEN TABLETS	Documentary Standards Support	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

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